Inhibition of mTOR attenuates store-operated Ca2+ entry in cells from endarterectomized tissues of patients with chronic thromboembolic pulmonary hypertension.

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Public Summary:

Scientific Abstract:
Pulmonary vascular remodeling occurs in patients with chronic thromboembolic pulmonary hypertension (CTEPH). One factor contributing to this vascular wall thickening is the proliferation of pulmonary artery smooth muscle cells (PASMC). Store-operated Ca(2+) entry (SOCE) and cytosolic free Ca(2+) concentration ([Ca(2+)](cyt)) in PASMC are known to be important in cell proliferation and vascular remodeling in pulmonary hypertension. Rapamycin is widely known for its antiproliferative effects in injured coronary arteries. Although several reports have suggested favorable effects of rapamycin in animal models of pulmonary hypertension, no reports have been published to date in human tissues. Here we report that rapamycin has an inhibitory effect on SOCE and an antiproliferative effect on PASMC derived from endarterectomized tissues of CTEPH patients. Cells were isolated from endarterectomized tissues obtained from patients undergoing pulmonary thromboendarterectomy (PTE). Immunohistochemical analysis indicated high deposition of platelet-derived growth factor (PDGF) in tissue sections from PTE tissues and increased PDGF receptor expression. PDGF transiently phosphorylated Akt, mammalian target of rapamycin (mTOR), and p70S6 kinase in CTEPH cells from CTEPH patients. Acute treatment (30 min) with rapamycin (10 nM) slightly increased cyclopiazonic acid (10 microM)-induced Ca(2+) mobilization and significantly reduced SOCE. Chronic treatment (24 h) with rapamycin reduced Ca(2+) mobilization and markedly inhibited SOCE. The inhibitory effects of rapamycin on SOCE were less prominent in control cells. Rapamycin also significantly reduced PDGF-stimulated cell proliferation. In conclusion, the data from this study indicate the importance of the mTOR pathway in the development of pulmonary vascular remodeling in CTEPH and suggest a potential therapeutic benefit of rapamycin (or inhibition of mTOR) in these patients.